THIS PAGE BLANK (USPTO)

Exhibit A

H-B-Vax II

Merck Sharp & Dohme (Aust.) Pty Ltd

(Distrib. CSL)

Permitted in sport

Pregnancy Category B2

Use: Immunisation against hepatitis B infection (all known subtypes) in individuals at risk

Contraindications: Intravenous, intradermal admin

Precautions: Immunodeficiency, immunosuppression; serious active infection; compromised cardiopulmonary status; high febrile or systemic reaction risk factor; postexposure prophylaxis;

pregnancy, children (dialysis formulation)

Adverse Reactions: Local pain and reactions; fatigue, headache, fever, GI upset; pharyngitis, URTI

H-B-Vax II Adult Formulation (Injection) Rx

Hepatitis B vaccine

Hepatitis B vaccine (recombinant). Hepatitis B surface antigen; aluminium hydroxide 0.5 mg (adsorbant), thiomersal 1:20,000; vaccine; Gluten free.

Pack(s): 10 mcg/mL .Fields[1]: $22.91

Pack(s): 10 mcg/mL .Fields[10]:

Dose: Adults (greater than or equal to 20 years): 3 x 1 mL doses IM in deltoid muscle; 1st dose at elected date, 2nd dose 1 month later, 3rd dose 6 months after 1st dose

H-B-Vax II Paediatric Formulation (Injection)

Rx

Hepatitis B vaccine

Hepatitis B vaccine (recombinant). Hepatitis B surface antigen; aluminium hydroxide 0.25 mg (adsorbant), thiomersal 1:20,000; vaccine; Gluten free.

Pack(s): 5 mcg/0.5 mL .Fields[1]: $16.15

Pack(s): 5 mcg/0.5 mL .Fields[10]:

Dose: 3 doses IM: 1st dose at elected date, 2nd dose 1 month later, 3rd dose 6 months after 1st dose. Children < 10 years: 0.25 mL each dose in anterolateral thigh. Adolescents (11-19 years): 0.5 mL each dose in deltoid muscle. Infants born of HBsAG positive mothers: see MIMS Annual

H-B-Vax II Dialysis Formulation (Injection) Rx

Hepatitis B vaccine

Hepatitis B vaccine (recombinant). Hepatitis B surface antigen; aluminium hydroxide 0.5 mg (adsorbant), thiomersal 1:20,000; vaccine; Gluten free.

Pack(s): 40 mcg/mL .Fields[1]: $54.41

Dose: Adults: 3 x 1 mL doses IM in deltoid muscle; 1st dose at elected date, 2nd dose 1 month later, 3rd dose 6 months after 1st dose

Composition

Adult formulation.

Each 1 mL dose of vaccine contains 10 microgram of hepatitis B surface antigen adsorbed onto approximately 0.5 mg aluminium hydroxide; thiomersal (mercury derivative) 1:20,000 added as a preservative.

Paediatric formulation.

Each 0.5 mL dose of vaccine contains 5 microgram of hepatitis B surface antigen adsorbed onto approximately 0.25 mg aluminium hydroxide; thiomersal (mercury derivative) 1:20,000 added as a preservative.

Dialysis formulation.

Each 1 mL dose contains 40 microgram of hepatitis B surgace antigen adsorbed onto approximately 0.5 mg of aluminium hydroxide; thiomersal (mercury derivative) 1:20,000 added as a preservative.

The vaccine is of the adw subtype.

Description

H-B-Vax II hepatitis B vaccine (recombinant) is a noninfectious subunit viral vaccine derived from surface antigen (HBsAg or Australia antigen) of hepatitis B virus produced in yeast cells.

The antigen is harvested and purified from fermentation cultures of a recombinant strain of the yeast Saccharomyces cerevisiae containing the gene for the adw subtype of HBsAg. The vaccine contains no detectable yeast DNA but may contain up to 1% yeast protein.

The vaccine against hepatitis B is free of association with human blood or blood products.

Actions

Pharmacology.

Immunogenicity.

Clinical studies have established that H-B-Vax II, when injected into the deltoid muscle, induced protective levels of antibody (defined as greater than or equal to 10 mIU/mL anti-HBs) in 96% of 1,213 healthy adults who received the recommended three dose regimen. Antibody responses varied with age; a

protective level of antibody was induced in 98% of 787 young adults 20 to 29 years of age, in 94% of 249 adults 30 to 39 years of age, and in 89% of 177 adults greater than or equal to 40 years of age. Studies with hepatitis B vaccine derived from plasma have shown that a lower response rate (81%) to vaccine

may be obtained if the vaccine is administered as a gluteal injection. Seroconversion rates and geometric mean antibody titres

were measured one to two months after the third dose.

In clinical studies, 99% of 94 infants under one year of age born of noncarrier mothers, 96% of 46 children one to ten years of age, and 99% of 112 adolescents 11 to 19 years of age developed a protective level of antibody following the recommended three dose regimen of vaccine.

Predialysis and haemodialysis patients respond less well to H-B-Vax II than do healthy individuals. In two studies, where 40 microgram doses of vaccine were administered in the deltoid muscle, 89% of 28 participants developed anti-HBs, with 86% achieving levels greater than or equal to 10 mIU/mL. Serological data on the proposed dosage regimen are limited to 28 subjects only; antibody levels achieved in these subjects were considerably lower than in normal subjects. No information is available on the persistence of antibodies in these subjects beyond six months after the last dose of the vaccine.

The protective efficacy of 5 microgram doses of H-B-Vax II has been demonstrated in neonates born of mothers positive for both HBsAg and HBeAg (a core associated antigenic complex which correlates with high infectivity). In a clinical study of infants who received one dose of Hepatitis B Immune Globulin at birth followed by the recommended three dose regimen of H-B-Vax II, chronic infection had not occurred in 96% of 130 infants after nine months of follow-up. The estimated efficacy in prevention of chronic hepatitis B infection was 95% as compared to the infection rate in untreated historical controls. Significantly fewer neonates became chronically infected when given one dose of Hepatitis B Immune Globulin at birth followed by the recommended three dose regimen of H-B-Vax II when compared to historical controls who received only a single dose of Hepatitis B Immune Globulin.

It has been demonstrated that doses of up to 3 mL of Hepatitis B Immune Globulin, when administered simultaneously with the first dose of H-B-Vax II at separate body sites, did not interfere with the induction of protective antibodies against hepatitis B virus elicited by the three dose vaccine regimen.

The duration of protective effect of H-B-Vax II is unknown at present, and the need for booster doses not defined.

Reports in the literature described a more virulent form of hepatitis B associated with superinfections or co-infections by delta virus, an incomplete RNA virus. Delta virus can only infect and cause illness in persons infected with hepatitis B virus since the delta agent requires a coat of HBsAg in order to become infectious. Therefore, persons immune to hepatitis B virus infection should also be immune to delta virus infection.

Indications

Immunisation against infection caused by all known subtypes of hepatitis B virus.

H-B-Vax II will not prevent hepatitis caused by other agents, such as hepatitis A virus, non-A non-B hepatitis viruses or other viruses known to infect the liver.

Vaccination is recommended in persons of all ages who are at substantial risk of hepatitis B virus infection and have been demonstrated or judged to be susceptible.

Contraindications

Hypersensitivity to any component of the vaccine.

Hypersensitivity to yeast (Saccharomyces cerevisiae). Patients who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of H-B-Vax II.

Precautions

Persons with immunodeficiency or those receiving immunosuppressive therapy require larger vaccine doses and respond less well than healthy individuals. Included in this group are haemodialysis patients for whom 40 microgram doses are recommended. (See Pharmacology.)

Because of the long incubation period for hepatitis B, it is possible for unrecognised infection to be present at the time H-B-Vax II is given. H-B-Vax II may not prevent hepatitis B in such patients.

Further study is required to determine the effectiveness of H-B-Vax II in preventing hepatitis when the vaccine regimen is begun after an exposure to the hepatitis B virus has already occurred (i.e. use for postexposure prophylaxis). Information available so far suggests that efficacy is reduced in such cases.

As with any parenteral vaccine, adrenaline should be available for immediate use should anaphylaxis or an anaphylactoid reaction occur.

Any serious active infection is reason for delaying use of H-B-Vax II except when, in the opinion of the doctor, withholding the vaccine entails a greater risk.

Caution and appropriate care should be exercised in administering H-B-Vax II to individuals with severely compromised cardiopulmonary status or to others in whom a febrile or systemic reaction could pose a significant risk.

Use in pregnancy.

(Category B2)

There is no convincing evidence of risk to the fetus from immunisation of pregnant women using inactivated virus vaccines, bacterial vaccines, or toxoids.

Animal reproduction studies have not been conducted with H-B-Vax II. It is not known whether H-B-Vax II can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. H-B-Vax II should be given to a pregnant woman only if clearly needed.

Use in lactation.

It is not known whether H-B-Vax II is excreted in human milk. However, studies with H-B-Vax II in 12 lactating women have failed to reveal evidence of this vaccine being secreted.

Use in children. ——

H-B-Vax II has been shown to be immunogenic and usually well tolerated in infants and children of all ages. Newborn infants also respond well; maternally transferred antibodies do not interfere with the active immune response to the vaccine. See Dosage and Administration for recommended paediatric dosage and for recommended dosage for infants born to HBsAg positive mothers.

The safety profile and effectiveness of the dialysis formulation in children have not been established.

Adverse Reactions

H-B-Vax II is generally well tolerated. No serious adverse reactions attributable to the vaccine have been reported during the course of clinical trials. No serious hypersensitivity reactions have been reported. No adverse experiences were reported during clinical trials which could be related to changes in the titres of antibodies to yeast. As with any vaccine, there is the possibility that broad use of the vaccine could reveal adverse reactions not observed in clinical trials.

The following adverse reactions were reported in clinical studies in healthy adults.

More common reactions.

(greater than or equal to 1% of injections.) Local reaction (injection site).

Injection site reactions (26% of doses) consisting principally of local pain, soreness, tenderness, pruritus, erythema, ecchymosis, swelling, warmth, and nodule formation.

Body as a whole.

The most frequent systemic complaints include fatigue/asthenia (4.2%), fever greater than or equal to 37.8 deg. C (3.2%), malaise (1.2%).

Gastrointestinal.

Nausea (1.8%), diarrhoea (1.1%).

Nervous system.

Headache (4.1%).

Respiratory.

Pharyngitis (1.2%), upper respiratory infection (1.0%).

Less common reactions.

(< 1% of injections.) Body as a whole.

Sweating, achiness, sensation of warmth, lightheadedness, chills, flushing.

Gastrointestinal.

Vomiting, abdominal pains/cramps, dyspepsia, diminished appetite.

Respiratory.

Rhinitis, influenza, cough.

Nervous system.

Vertigo/dizziness, paraesthesia.

Dermatological.

Pruritus, rash (nonspecified), angioedema, urticaria.

Musculoskeletal.

Arthralgia including monoarticular, myalgia, back pain, neck pain, shoulder pain, neck stiffness.

Lymphatic.

Lymphadenopathy.

Psychiatric/behavioural.

Insomnia/disturbed sleep.

Special senses.

Earache.

Genitourinary.

Dysuria.

Cardiovascular.

Hypotension.

The following additional adverse reactions have been reported with use of the marketed vaccine; however, in many instances a causal relationship to the vaccine has not been established.

Hypersensitivity.

Anaphylaxis and symptoms of immediate hypersensitivity reactions including oedema, dyspnoea, chest discomfort, bronchial spasm, or palpitation have been reported within the first few hours after vaccination. An apparent hypersensitivity syndrome (serum sickness-like) of delayed onset has been reported days to weeks after vaccination, including arthritis (usually transient) and dermatological reactions such as erythema multiforme, ecchymoses and erythema nodosum (see Precautions).

Nervous system.

Peripheral neuropathy including Bell's palsy; Guillain-Barre syndrome, optic neuritis.

Special senses.

Tinnitus.

Haematological.

Increased erythrocyte sedimentation rate.

Infants and young children.

The nature and incidence of systemic adverse reactions is different in infants and young children. In clinical studies, in infants up to one year of age and children one to ten years of age, reactions reported greater than or equal to 1% of doses given in studies were as follows.

Ages 0 to 1 years: irritability (3.2%), fever greater than or equal to 38.3 deg. C (2.8%), diminished appetite (2.8%), diarrhoea (2.5%), vomiting (1.8%), cough (1.4%), cold symptoms (1.1%).

Ages 1 to 10 years: cold symptoms (2.7%), viral infection (2.7%), fever greater than or equal to 38.3 deg. C (2.1%), cough (2.1%), injection site reactions (1.6%), diarrhoea (1.1%), rhinitis (1.1%), headache (1.1%).

Potential adverse effects.

In addition, a variety of adverse effects not observed in clinical trials with H-B-Vax II have been reported with H-B-Vax (plasma derived hepatitis B vaccine). Those listed below are to serve as alerting information to doctors.

Body as a whole.

Hypersensitivity. Irritability.

Nervous system.

Neurological disorders such as myelitis, including transverse myelitis; acute radiculoneuropathy and Herpes zoster.

Haematological.

Thrombocytopenia.

Special senses.

Visual disturbances.

Dosage and Administration

Do not inject intravenously or intradermally.

H-B-Vax II is for intramuscular injection. The deltoid muscle is the preferred site for intramuscular injection in adults. Data suggest that injections given in the buttocks are frequently given into fatty tissue instead of into muscle. Such injections have resulted in a lower seroconversion rate than was expected. The anterolateral thigh is the recommended site for intramuscular injection in infants and young children.

As the plasma derived vaccine has been shown to be immunogenic by the subcutaneous route, H-B-Vax II may also be administered subcutaneously to persons at risk of haemorrhage following intramuscular injections. However, when other aluminium adsorbed vaccines have been administered subcutaneously, an increased incidence of local reactions including subcutaneous nodules has been observed. Therefore,

subcutaneous administration should be used only in persons (e.g. haemophiliacs) at risk of haemorrhage following intramuscular injections.

Shake well before withdrawal and use. Thorough agitation at the time of administration is necessary to maintain suspension of the vaccine.

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis and other infectious agents from one person to another.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. After thorough agitation, H-B-Vax II is a slightly opaque, white suspension. The immunisation regimen consists of three doses of vaccine given according to the following schedule. First dose: at elected date; second dose: one month later; third dose: six months after the first dose.

The volume of vaccine to be given on each occasion appears in Table 1. Please refer to table 1.

Revaccination.

The duration of protective effect of H-B-Vax II is unknown at present, and the need for booster doses is not yet defined. One 10 microgram dose of H-B-Vax II induced an anamnestic response in 94% of 31 healthy adults who had been vaccinated five to seven years previously with H-B-Vax II (Hepatitis B Vaccine).

Whenever revaccination or administration of a booster dose is appropriate, H-B-Vax II may be used (see Actions, Pharmacology).

Dosage for infants born of HBsAg positive mothers.

(See Actions, Pharmacology.)

Results from clinical studies indicate that administration of one 0.5 mL dose of Hepatitis B Immune Globulin at birth and three 5 microgram (0.5 mL) doses of H-B-Vax II, the first dose given within one week after birth, was 96% effective in preventing establishment of the chronic carrier state in infants born to HBsAg and HBeAg positive mothers. Testing for HBsAg and anti-HBs is recommended at 12 to 15 months to monitor the final success or failure of therapy. If HBsAg is not

detectable, and anti-HBs is present, the child has been protected. The recommended treatment regimen for infants born of HBsAg positive mothers follows. Please refer to table 2.

*The first 0.5 mL dose of H-B-Vax II may be given at birth at the same time as Hepatitis B Immune Globulin, but should be administered in the opposite anterolateral thigh. This procedure may be preferable to ensure absorption of the vaccine.

Testing for HBsAg and anti-HBs is recommended at 12 to 15 months to monitor the final success or failure of therapy. If HBsAg is not detectable, and anti-HBs is present, therapy can be considered successful.

Known or presumed exposure to HBsAg.

There are no prospective studies directly testing the efficacy of a combination of Hepatitis B Immune Globulin (Human) and H-B-Vax II in preventing clinical hepatitis B following percutaneous, ocular or mucous membrane exposure to hepatitis B virus. However, since most persons with such exposure (e.g.

healthcare workers) are candidates for H-B-Vax II and since combined Hepatitis B Immune Globulin (Human) plus vaccine is more efficacious than Hepatitis B Immune Globulin (Human) alone in perinatal exposures, the following guidelines are recommended for persons who have been exposed to hepatitis B

virus (e.g. through percutaneous (needlestick), ocular or mucous membrane exposure to blood known or presumed to contain HBsAg; human bites by known or presumed HBsAg carriers, that penetrate the skin; or following intimate sexual contact with known or presumed HBsAg carriers).

Hepatitis B Immune Globulin (Human) (0.06 mL/kg) should be given intramuscularly as soon as possible after exposure and within 24 hours if possible. H-B-Vax II (see dosage recommendation) should be given intramuscularly at a separate site within seven days of exposure and second and third doses given one and six months, respectively, after the first dose.

Administration.

Withdraw the recommended dose from the vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents.

Presentation

Paediatric.

Vial, 5 microgram/0.5 mL: 1's, 10's.

Adult.

Vial, 10 microgram/1 mL: 1's, 10's.

Dialysis.

40 microgram/1 mL: 1's.

Storage

Store at 2 to 8 deg. C. (Refrigerate. Do not freeze.) Storage above or below the recommended temperature may reduce potency.

Poisons Schedule

S4.